UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/216,641	12/17/1998	TERRY LEE BURKOTH	7010-0001	9355

7590 07/16/2002

Thomas P. McCracken
POWDERJECT PHARMACEUTICALS PLC
Florey House, Oxford Science Park
Oxford, GBN OX44GA
UNITED KINGDOM

EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/216,641	Applicant(s) BURKOTH ET AL.	
	Examiner Q. Nguyen	Art Unit 1636	

-- The MAILING DATE of this communication app ars on th cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-20,23-27 and 29-40* is/are rejected.

7)☒ Claim(s) *21,22 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 03/13/02 in Paper No. 13 has been entered.

Claims 1-40 are pending in the present application. Claims 1-14 are withdrawn from further consideration because they are drawn to the non-elected invention. Claims 15-40 are examined on the merits herein.

This application contains claims 1-14 drawn to an invention nonelected without traverse in Paper No. 6. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Response to Amendment

The rejection of claims 15, 21 and 22 under 35 U.S.C. 103(a) as being unpatentable over Bellhouse et al. (U.S. Patent No. 5,630,796) in view of King et al. (U.S. Patent No. 5,486,364) and Gergely et al. (U.S. Patent No. 4,737,366) is withdrawn.

Claim Rejections - 35 USC § 112

Claims 15-20, 23-28, 37 and 40 (the claim is dependent on claim 40) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method for forming densified particles from a particular pharmaceutical preparation containing a peptide or a protein or a gene construct, comprising pressing or grinding said pharmaceutical preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection; the same densified or compacted particular pharmaceutical composition and a unit dosage container for a needleless syringe comprising the same;

(2) A method of delivering a selected pharmaceutical agent to a vertebrate subject, said method comprising providing a compacted particulate pharmaceutical preparation according to claim 37, said preparation comprising the pharmaceutical agent and delivering the preparation to a target tissue or cell of the vertebrate subject by needless syringe, wherein said pharmaceutical agent is a peptide or a protein;

(3) A method of delivering a gene construct encoding an antigen to a vertebrate subject, said method comprising providing a compacted particulate preparation formed from a porous preparation, said compacted composition having an average particle size in the range of 0.1 to 250 μm mean diameter, a particle density in the range of 0.1 to 25 g/cm^3 and said gene construct, and transdermally delivering the preparation to the vertebrate subject by needless syringe, wherein said gene construct elicits an immune response in said vertebrate subject;

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make or use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action.

Claims 15-20 and 23-28 are drawn to a method for forming densified particles from a particulate pharmaceutical preparation, comprising compacting the preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection. Claim 40 is directed to a method of delivering a selected pharmaceutical agent to a vertebrate subject, said method comprising providing the same compacted particulate pharmaceutical preparation and delivering to a target tissue or cell of the vertebrate subject by needleless syringe.

With regard to the nature of the instant claims, the specification discloses compositions comprising pGREEN-1 or a human growth hormone (hGH) or β-galactosidase expression vector plasmid with trehalose sugar excipient, which were compressed, ground and sieved to form condensed nucleic acid compositions. The compositions were individually administered through a needleless injection device to target skin surfaces of either C57BL/10 mice or female pigs. After 24 hours of administration, biopsy samples revealed GFP and β-galactosidase expression in treated sites, whereas hGH expression was not detected. The lack of hGH expression was attributed to the low loading density of the nucleic acid in the composition (See example 2). The specification further teaches the preparation of a densified composition comprising lyophilized recombinant hGH powder (Genotropin), and it demonstrates that in comparison with the lyophilized rhGH powder, a higher proportion of the densified

composition penetrated porcine skin by needleless injection. Additionally, the specification teaches that markedly increased blood serum levels of rhGH were obtained in New Zealand White rabbits that were intradermally administered with densified Genotropin particles through the needleless injection system.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

Regarding to claims 15-20 and 23-28, as written the claims encompass any forms or means of compacting a particulate pharmaceutical preparation that may contain a peptide or protein or a gene construct. Apart from the teachings for pressing a porous pharmaceutical preparation under high pressure (e.g., via hydraulic press, tablet press or rotary press) which is an essential and critical element of the presently claimed invention, the instant specification fails to teach any other forms or means of compacting a particulate pharmaceutical preparation as encompassed by the broad scope of the instant claims. As such, it would have required undue experimentation for one skilled in the art to make and use the method as broadly claimed on the basis of the instant disclosure.

With respect to the method claim encompassing a densified pharmaceutical preparation containing a gene construct having the recited physical characteristics, when read in light of the specification the sole purpose for such a delivery method is for gene therapy and genetic immunization (See pages 22-24 of the specification). It is unclear whether the gene construct in the densified pharmaceutical preparation of the

present invention is still intact and that it is not susceptible to nicks or degradation due to the compacting process under high pressure, specifically at about 1,000 to 24,000 pounds per square inch, such that the pharmaceutical preparation has any beneficial use. A genetic construct in the form of a nucleic acid or DNA molecule is highly sensitive to degradation, particularly for a large genetic construct. This is a particular concern since the instant specification clearly indicates a lack of hGH expression being detected in treated mice or pigs upon administering into said animals a preparation containing an expression plasmid encoding hGH (the only example using a therapeutically relevant encoded molecule) by a needleless injection (See example 2). Furthermore, as enablement requires the specification to teach how to make and **use** the claimed invention, the instant specification fails to enable the **use** of the densified particulate pharmaceutical composition comprising a gene construct for gene therapy and genetic immunization.

Regarding to the gene therapy aspect encompassed by the pharmaceutical scope of the method claim, at the effective filing date of the present application, gene therapy was considered to be immature and highly unpredictable (Dang et al., Clin. Cancer Res. 5:471-474, 1999; Cited previously). The instant specification is not enabled for the use of the claimed invention because it fails to provide sufficient guidance for one skilled in the art on the use of the compact or densified particulate pharmaceutical composition comprising of a gene construct of the present invention to obtain any therapeutic effects contemplated by Applicants. As noted above, it is unclear whether the gene construct in the densified pharmaceutical preparation is intact and

that it is not susceptible to nicks or degradation due to the compacting process under high pressure, or during its delivery to a subject by needleless injection. A genetic construct in the form of a nucleic acid or DNA molecule is highly sensitive to degradation, particularly for a large genetic construct. Applicants have noted that known biolistic techniques are not appropriate for use with large DNA molecules since precipitation of such molecules onto core carriers can lead to unstable configurations that will not withstand the shear forces of gene gun delivery (specification, page 7, line 32 continues to line 2 of page 8). Additionally, and more importantly there is no correlation between the expression of green fluorescent protein (GFP) or β-galactosidase with the desired therapeutic results for treating a plethora of diseases, disorders, genetic defects such as, AIDS, cancer, neurological diseases, cardiovascular diseases, cystic fibrosis, adenosine deaminase deficiency among many others as contemplated by Applicants. There is no evidence of record that the densified pharmaceutical composition comprising a gene construct in the present application could provide any expression of a relevant therapeutic gene product *in vivo* at any level via a needleless injection, let alone a therapeutic expression level. There are several known factors limiting an effective gene therapy, and these include sub-optimal vectors, the lack of a long-term and stable gene expression *in vivo*, as well as the lack of an efficient gene delivery to target tissues (Dang et al., 1999). It is well known in the art that transgene expression *in vivo* is very transient. As examples, Palmer et al. (Proc. Natl. Acad. Sci. 88:1330-1334, 1991) demonstrated that the *in vivo* expression of human factor IX by transplanted syngeneic recombinant fibroblasts was transient and

vanished 1-5 weeks post-transplantation. Riddell et al. (Nature Med. 2:216-223, 1996) reported that five out of six patients seropositive for human immunodeficiency virus developed cytotoxic T-lymphocytes responses specific to a novel protein and eliminated infused autologous CD8+ HIV-specific cytotoxic T cells transduced with a fusion suicide gene (See abstract). Given the lack of guidance or direction provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and **use** the instant broadly claimed invention.

With regard to the nucleic acid immunization aspect encompassed by the pharmaceutical scope of the method claim, the state of the art was also new and unpredictable at the effective filing date of the present application. Chattergoon et al. (FASEB J. 11:753-763, 1997) stated that "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology is considered an emerging technology" (column 1, paragraph 2, page 762). More recently, Leitner et al. (Vaccine 18:765-777, 2000) further stated "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Leitner et al. also listed several variable factors affecting the immunogenicity of genetic vaccines. These include: the structure of the plasmid backbone, amount of plasmid delivered, expression levels of the antigen, age and strain of the particular species, target tissue, and route of immunization among others (See Table 1, page 767). The instant specification fails to provide sufficient guidance for a skilled artisan on how to achieve any therapeutic vaccination using the densified particulate pharmaceutical

composition comprising a gene construct of the present invention. As such, it would have required undue experimentation for a skilled artisan to make and use the full breath of the method as claimed.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Furthermore, claim 40 encompasses the delivery of a compacted particulate pharmaceutical preparation containing a pharmaceutical agent to a target tissue or cell of a vertebrate subject by any routes of administration such as intravenous, oral or aerosol deliveries using a needleless syringe. However, apart from the transdermal delivery of the pharmaceutical preparation taught by the present application, the specification fails to provide sufficient guidance for one skilled in the art on how to make and use the method as claimed broadly, especially for achieving therapeutic effects. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so. Moreover, as noted above the physiological art is recognized as unpredictable. Given the lack of guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the method as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability and current state of the gene therapy, nucleic acid immunization and physiological arts in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and **use** the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 03/13/02 in Paper No. 13 (pages 6-13) have been fully considered.

With respect to the issue of means of compacting the particulate pharmaceutical preparations, Applicants referred to various passages in the instant specification to what is meant by compaction, and argued that the critical feature of the presently claimed invention is that compaction of typically porous starting materials results in a reduction of porosity and a corresponding increase in the bulk density of the densified material. Applicants further argued that these methods have been demonstrated throughout the specification using disparate molecules, including working examples. Therefore, it would not have required undue experimentation for a skilled artisan to make and use the methods as claimed. Applicants' arguments are respectfully found unpersuasive because the term "compacting" is not defined in the specification, for example, by compacting we mean, and that condensing the nucleic acid powders produced by lyophilization and spray-drying techniques can be conducted by compaction in a suitable press (e.g., hydraulic press, tablet press or rotary press) is the only means of

compacting that can be found in the referred passages. However, it is noted that the claims simply recite "compacting the preparation", not necessarily limiting to a means of compacting using a suitable press or the preparation is limited to low density particulate solids produced by lyophilization or spray-drying techniques as taught by the instant specification. Moreover, since the active steps involved in compacting the preparation are not recited in the claims, it is reasonable for Examiner to interpret the claims broadly to encompass any means that results the preparation into a compact form. As such, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

With respect to the lack of expression demonstrated for a densified gene construct encoding hGH in Example 2, Applicants argued that the lack of expression was not due to some denaturation event rather due to too small of a dose being administered. Applicants also argued "the entire industry uses marker gene expression as a direct correlate to therapeutic gene expression. This is simply how research is carried out in the industry". Applicants further assert that the instant specification is fully enabled for claims drawn to a densified particulate pharmaceutical composition containing a gene construct and methods of making and using the same. With regard to routes of delivery in claim 40, Applicants also argued "Applicants' specification contains within it a connotation of how to use the invention, and the art recognizes that standard modes of administration are known and contemplated, then 35 U.S.C. 112, first paragraph, is satisfied". Applicants' arguments are respectfully found to be

unpersuasive because although a densified particulate composition containing a gene construct of the instant invention can be made, but the therapeutic effects resulting from the use of such densified particulate composition has never been demonstrated in the present disclosure. At the effective filing date of the present application, the attainment of therapeutic effects via gene therapy in general was highly unpredictable as evidenced by the teachings of Dang et al. The sole *in vivo* example using a densified particulate composition containing a therapeutically relevant gene construct (hGH) failed to demonstrate the expression hGH, let alone attaining any therapeutic effects. Applicants fail to provide any objective evidence to confirm that the lack of hGH expression is due to a too small dosage used and not due to other factors. It is noted that it does not take an undue experimentation for one to use a larger dosage in the same experiment, and it is unclear to the Examiner why the same dosage as the preparation containing a gene construct encoding for a marker gene was not utilized. Moreover, with respect to the breadth of the desired therapeutic results for treating a plethora of diseases, disorders, genetic defects such as, AIDS, cancer, neurological diseases, cardiovascular diseases, cystic fibrosis, adenosine deaminase deficiency among many others as contemplated by Applicants, and given the guidance provided by the instant specification it would have required undue experimentation for a skilled artisan to use the instant broadly claimed invention. With respect to claim 40, the instant specification fails to provide sufficient guidance for a skilled artisan on how to obtain any therapeutic effects through a particular route of administration, let alone through any route of delivery as encompassed by the breadth of the claim. Even in

1999, many years after the effective filing date of the present application, Dang et al. stated that "Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (page 474, col. 2, last paragraph). With the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

With respect to the cited references of Palmer et al. and Riddell et al., Applicants failed to see the relevance of these references and requested for clarification. These references indicate that the expression of a transgene *in vivo* is unstable, one of several factors responsible for the unpredictability in obtaining therapeutic effects via gene therapy. As such, with the lack of guidance provided by the present specification, particularly without any relevant *in vivo* example (part of guidance) in an unpredictable gene therapy art, it would have required undue experimentation for a skilled artisan to obtain therapeutic effects for a plethora of diseases, disorders, genetic defects such as, AIDS, cancer, neurological diseases, cardiovascular diseases, cystic fibrosis, adenosine deaminase deficiency among many others as contemplated by Applicants via the use of the pharmaceutical preparation containing a gene construct of the presently claimed invention.

With respect to the issue of nucleic acid immunization, Applicants argued "Nucleic acid immunization has been carried out for over a decade now, with multiple preclinical and clinical trials demonstrating time and again that delivered gene

constructs are both expressed and provide a meaningful immune response in all sorted of animals models and in man". Applicants' argument is respectfully found unpersuasive because Applicants have failed to provide any objective evidence indicating or suggesting that therapeutic and prophylactic effects could be routinely obtained via nucleic acid immunization, particularly at the effective filing date of the present application. Applicant's argument is in direct contrast to the assessment of the state of genetic immunization for attaining therapeutic effects by Chattergoon et al. and Leitner et al. discussed above. However, at the effective filing date of the present application Examiner acknowledges that it does not require undue experimentation for a skilled artisan to elicit an immune response in a host via transdermal delivery of a preparation containing a gene construct encoding for an antigen, and this is the scope given.

Accordingly, claims 15-40 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Claim Rejections - 35 USC § 102

Claims 15-20, 23-27, 29-31, 33-37 and 39-40 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bellhouse et al. (U.S. Patent No. 5,630,796).

The claims are drawn to a method for forming densified particles from a particulate pharmaceutical preparation, comprising compacting the preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation into densified particles of suitable size and density for transdermal delivery

thereof by needleless injection; a composition of a densified particulate pharmaceutical composition formed from a lyophilized or spray-dried pharmaceutical composition preparation, said densified composition having an average particle size in the range of about 0.1 to 250 μm mean diameter and a particle density in the range of 0.1 to 25 g/cm^3; a unit-dosage container for a needless syringe comprising the same composition. Claim 40 is directed to a method of delivering a selected pharmaceutical agent to a vertebrate subject, said method comprising providing the same compacted particulate pharmaceutical preparation of claim 37 and delivering to a target tissue or cell of the vertebrate subject by needleless syringe.

Bellhouse et al. teach a method for preparing as well as delivering transdermally into a mammalian subject particles of a powdered therapeutic agent (e.g., protein, analgesics, hormones, drugs such as insulin and calcitonin) that is ground (a form of compacting the powdered therapeutic agent with a pestle and mortar as shown in example 1 of the instant specification) and sieved to a precise diameter (col. 4, lines 13-14 and example 2) using a needless syringe. The particles have a size of between 0.1 and 250 μm, preferably for transdermal powdered drug injection of between 1 and 50 μm, and more preferably between 10 and 20 μm (a typical cell size). Furthermore, the particles have a density in the range between 0.1 and 25 g/cm^3, for transdermal drug injection, preferably in the range between 0.5 and 2.0 g/cm^3, and more preferentially 1.0 g/cm^3 (col. 3, line 66 continues to line 8 of col. 4). Additionally, Bellhouse et al. teach that a substantially inert carrier may have to be included to provide the particles with the required size and mass for adequate penetration, particularly if the therapeutic agent is

potent or of low density (col. 4, lines 19-22). Bellhouse et al. further disclose that standard currently available techniques such as lyophilisation or free-drying, spray-drying, emulsifying, drying in the presence of trehalose and the like can be used to stabilise an agent, a whole cell for an embodiment of the issued patent, prior to direct injection into the body (col. 2, lines 52-60). Because the pharmaceutical composition disclosed by Bellhouse et al. has the same characteristics such as particle size, particle density suitable for transdermal delivery into a mammalian subject using a needleless injector as those of the present invention, Bellhouse et al. anticipate the instant claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 03/13/02 in Paper No. 13 (pages 15-17) have been fully considered.

Applicants argued that the term "grinding" used in Bellhouse (U.S. Patent No. 5,630,796) is used as a way to comminute a powder into smaller particles, not to increase density. Applicants further argued that if grinding was suitable for increasing the density of the smaller particles, then why Bellhouse also teaches that carriers must be used to increase mass of agents having low density. Applicants also argued that in the present application, Applicants disclosed that grinding is used to size reduce a compacted material, and that when spray-dried and lyophilized pharmaceutical particles are ground or milled, they yield very small, light and non-dense particles that are poorly suited for delivery through skin or mucosal tissues. Applicants also argued that the

pharmaceutical powders disclosed by Bellhouse do not have the same characteristics as applicants' recited compacted compositions. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, according to the Merriam-Webster's Collegiate Dictionary, Tenth Edition, the term "grind" or "ground" is defined as to press together with a rotating motion or to rub or press harshly; and the term "compact" is defined as to press together or to become compacted (see attachment), therefore grinding is an equivalent form of compacting the powdered therapeutic agent. Furthermore, in example 1 of the instant specification freeze-dried DNA-tetrahose solid were milled using an agate mortar and pestle (equivalent to grinding) to form the microparticles suitable for needleless injection, and Applicants acknowledged on the record that these microparticles are densified particles as evidenced the statement "In Example 1, a densified gene construct encoding the beta-galactosidase marker was delivered into cells" (page 10, lines 2-5).

Secondly, although Bellhouse teaches that carriers must be used to increase mass of agents having low density, this does not negate the fact that grinding would not result in the formation of densified particles for certain powdered therapeutic agents as evidenced by example 1 of the present disclosure. Grinding may not be sufficient to densify particles of low density, but that does not mean that grinding would not result in densified particles derived from non-low density powdered therapeutic agents. It is noted that the instant claims do not recite anything regarding to the density of the starting pharmaceutical preparation.

Thirdly, with respect to Applicants' argument that spray-dried and lyophilized pharmaceutical particles that are ground or milled, they yield very small, light and non-dense particles that are poorly suited for delivery through skin or mucosal tissues, do Applicants really question the enablement of the claims in the issued Bellhouse patent?

Fourthly, Applicants fail to provide any objective evidence or scientific reasoning why the pharmaceutical powders disclosed by Bellhouse do not have the same characteristics as applicants' recited compacted compositions. It is noted that the pharmaceutical powders taught by Bellhouse have a size of between 0.1 and 250 μm, 1 and 50 μm, or 10 and 20 μm (a typical cell size), as well as a density in the range between 0.1 and 25 g/cm^3, 0.5 and 2.0 g/cm^3 or 1.0 g/cm^3 (col. 3, line 66 continues to line 8 of col. 4, and the claims) which are encompassed within the size and density ranges of the presently claimed compacted compositions.

Accordingly, claims 15-20, 23-27, 29-31, 33-37 and 39-40 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bellhouse et al. (U.S. Patent No. 5,630,796) for the reasons set forth above.

Claims 29, 30 and 32-39 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bellhouse et al. (U.S. Patent No. 6,010,478).

It is noted for a composition claim, the intended use is not given any patentably weight. Bellhouse et al. teach that particles of a DNA or RNA molecule, are prepared as compositions which can contain one or more added materials such as carriers, vehicles, and/or excipients to increase the amount of solids in particulate compositions

for delivering into skin or mucosal tissue using a needleless syringe. Examples of excipients include pharmaceutical grades of dextrose, sucrose, lactose, trehalose, manitol and others (see the entire patent, particularly col. 4, lines 59-64; col. 5, lines 2-15; and col. 10, lines 36-45). Additionally, Bellhouse et al. teach that the particles have an approximate size generally ranging from 0.1 to 250 μm and for gene delivery, the particle size is generally substantially smaller than 10 μm (col. 10, lines 17-23). Furthermore, the particles have densities in the range between about 0.1 and 25 g/cm^3 for use in needleless injection (col. 10, lines 32-35).

Therefore, the reference anticipates the instant claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 03/13/02 in Paper No. 13 (page 19) have been fully considered.

Applicants mainly argued that the cited Bellhouse reference (U.S. Patent No. 6,010,478) is not a proper 102(e) reference because it does not have a priority date prior to Applicants' priority date of 11 September 1996. Applicants' argument is not found to be persuasive because the instant claims do not enjoy the priority date of 11 September 1996 because Applicants have failed to provide the priority paper 9619002.0 filed in Great Britain on 11 September 1996 in the present application. As such, the filing date of 14 August 1997 for the Bellhouse reference qualifies it as a 102(e) reference.

Accordingly, claims 29, 30 and 32-39 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bellhouse et al. (U.S. Patent No. 6,010,478).

Conclusions

Claims 21-22 and 28 are objected because they are dependent on rejected claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER